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Biguanide scaffold: Chemistry, Stability and Pharmacophoric Features For Drug Discovery

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ABSTRACT

Around the world, biguanides like metformin are often used to treat type-2 diabetes. Biguanides were created as a result of the discovery of guanidine and similar substances in the French lilac plant (Galegaofficinalis L.). Using the common medication metformin, the produced compounds were tested for their anti-diabetic properties. Drugs' mechanisms of action are determined by their electrical and structural makeup. Pharmacophoric feature detection is aided by accurate structural depiction of medications. Although biguanide derivatives are a significant class of pharmaceuticals, little is known about their electrical structure. The most often given medication for type II diabetes and associated conditions is metformin; nonetheless, the lack of structural evidence has hindered molecular understanding of its method or modes of action. Despite being underrepresented, the quantity of "success stories" involving compounds containing biguanides highlights their worth and untapped potential as effective metal ligands or future medications in a variety of therapeutic areas. Many biguanide derivatives, such as 1,1-dimethyl biguanide (metformin), phenylethylbiguanide (phenformin), and N-(4-chlorophenyl)-N0-(isopropyl)-imidodicarbonimidicdiamide (proguanil), are used as antihyperglycemic and antimalarial medications; however, no common mechanism has been proposed for these contentious therapeutic actions.The numerous therapeutic uses of medications containing biguanide groups, including antimalarial, antidiabetic, antiviral, anticancer, antibacterial, antifungal, anti-tubercular, antifilarial, anti-HIV, and other biological activities, are discussed in this review along with the research and development done on biguanides.

Keywords: *Biguanide, Anti-diabetic, Guanidine, Urea, Glargine, Activated Protein kinase, Escherichia coli, Dihydrofolatereductase(ecDHFR)*

1. INTRODUCTION

A chronic metabolic disease called diabetes mellitus (DM) is typified by elevated blood glucose levels brought on by deficiencies in either the action or synthesis of insulin, or both. Type 1 diabetes mellitus (T1DM), an autoimmune disease that causes the death of the pancreatic beta cells that produce insulin, and the more common type 2 diabetes mellitus (T2DM), which is linked to insulin resistance and frequently associated with obesity and lifestyle factors, are the two main types of the condition [1].

The prevalence of diabetes has significantly increased over the past few decades, with the World Health Organization (WHO) reporting that the number of adults living with diabetes has nearly doubled since 1980, rising from 108 million to approximately 422 million in 2014. This rise in prevalence is attributed to various factors, including genetic predisposition, lifestyle changes and environmental influences.[2,3]

Diabetes is associated with numerous complications, including cardiovascular disease, kidney failure, and neuropathy, making it a major public health concern globally.In order to effectively treat diabetes, dietary and physical activity changes must be combined with pharmaceutical therapies to regulate blood sugar levels and avoid complications.[4,5]

Understanding the complexities of diabetes, including its risk factors and treatment options, is essential for improving health outcomes and reducing the burden of this chronic disease on individuals and healthcare systems worldwide.[6]

2. MEDICATION OF DIABETES TREATMENT:

- **Insulin Therapy**.

- Rapid-acting insulin (e.g., Lispro, Aspart): Onset within minutes; used for mealtime
- Short-acting insulin (e.g., Regular): Onset in 30 minutes; also used for mealtime but with a longer duration
- Intermediate-acting insulin (e.g., NPH): Onset in 1-2 hours; provides basal insulin coverage.
- Long-acting insulin (e.g., Glargine, Detemir): Onset in 1-2 hours; provides a steady level of insulin.
- Ultra-long-acting insulin (e.g., Degludec): Lasts up to 42 hours; provides flexible dosing.

Mechanism: Insulin encourages muscle and fat cells to absorb glucose, which reduces blood glucose levels.[7]

Biguanides:

- Example: Metformin.
- **Mechanism:**Reducedhapatic glucose synthesis raises peripheral tissue insulin sensitivity and may reduce intestinal glucose absorption.
- **Indications:** First-line treatment for T2D, particularly in overweight patients.[8]

Sulfonylureas:

- Examples: Glipizide, Glyburide, Glimepiride.
- **Mechanism:**Close potassium channels that are sensitive to ATP to increase the release of insulin from pancreatic beta cells.
- **Indications:** Often used in T2D patients who are not achieving glycemic control with lifestyle changes or metformin.
- **Side Effects:** Risk of hypoglycemia and weight gain.[9]

Thiazolidinediones (TZDs)

- **Examples**: Pioglitazone, Rosiglitazone.
- **Mechanism**: Increase muscle and adipose tissue's sensitivity to insulin via activating peroxisome proliferator-activated receptor-gamma (PPAR-γ).
- **Indications**: Used for T2D management; effective in reducing insulin resistance.
- **Side Effects:**Edema, weight gain, and heightened heart failure risk.[10]

DPP-4 Inhibitors:

- Sitagliptin, Saxagliptin, Linagliptin.
- **Mechanism:**Reducedipeptidyl peptidase-4 to raise incretin hormone levels, which promote insulin secretion and prevent the production of glucagon..
- **Indications:** Used for T2D management, often in combination with other agents.
- **Side Effects:** Generally well tolerated; rare risk of pancreatitis.[11]

GLP-1 Receptor Agonists:

- Examples: Liraglutide, Exenatide, Semaglutide.
- **Mechanism:**Reduce glucagon secretion and increase insulin secretion in response to meals by mimicking the incretin hormone GLP-1.
- **Indications:** Used for T2D; also beneficial for weight loss and cardiovascular health.
- **Side Effects:** Nausea, vomiting, and potential pancreatitis.[12]

SGLT2 Inhibitors:

- Examples: Canagliflozin, Dapagliflozin, Empagliflozin.
- **Mechanism:** Inhibit sodium-glucose co-transporter 2, leading to increased urinary glucose excretion.
- **Indications:** Effective for T2D management; also beneficial for heart failure and chronic kidney disease.
- **Side Effects:** Risk of urinary tract infections and dehydration.[13]

Amylin Analogues:

- Example: Pramlintide.
- **Mechanism :**Increases satiety, inhibits glucagon secretion, and slows stomach emptying.
- **Indications:** Used in conjunction with insulin for T1D and T2D.
- **Side Effects:** Nausea , vomiting , headache , and hypoglycemia.[14]

Biguanides

Biguanides are a class of chemical compounds that contain two guanidine groups connected by a central nitrogen atom. Their general structure is characterized by the formula **(HN C(NH)NH)**, with variations depending on the functional groups attached.Biguanides are polar, hydrophilic, and can form salts with acids due to their basic nature. This property enhances their solubility and bioavailability in water-based systems.[15,16]

3. CHEMICAL AND PHARMACOLOGICAL PROPERTIES OF BIGUANIDES:

3.1Chemical structure of biguanide:

Biguanides have a very electron-rich π-conjugated system and the functional moiety N–C(N)double bondN–C(N)double bondN. The majority of biguanides are found in open chain systems, although some cyclic biguanides have also been used in medicinal chemistry due to their active state. They are primarily used in the monoprotonated state in pharmaceutical chemistry due to their high basicity and electron richness.[17,18]

3.2 Electronic structure of biguanide

3.2.1. Tautomeric Forms:

Biguanide can exist in a total of 10 different tautomeric forms, which can be interconverted through unimolecular and bimolecular processes. The presence of hydrogen on the bridging nitrogen (N4) is less favorable, with tautomers lacking this hydrogen being relatively more stable than those with it.

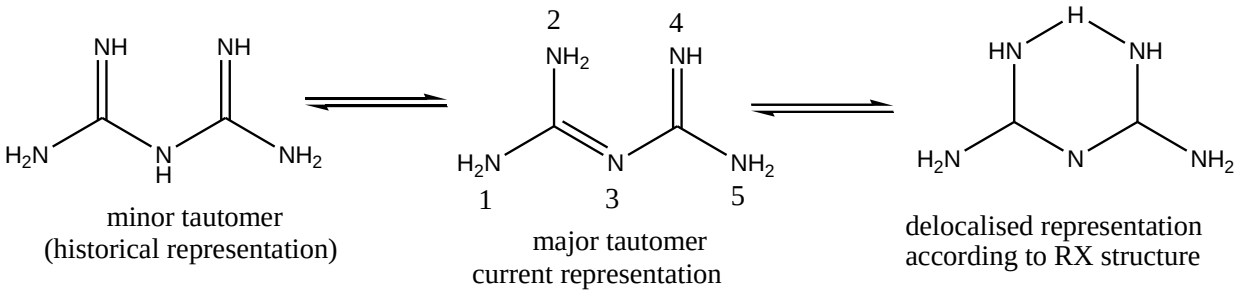

Figure : Tautomeric forms of biguanide

3.2.2. Electron Delocalization:

The electronic structure studies revealed significant electron delocalization in biguanide derivatives, which is crucial for understanding their basic nature and interactions with other molecules. This delocalization is enhanced upon protonation, affecting the compound's reactivity and stability.

3.2.3. Molecular Electrostatic Potential (MESP):

In their most stable configurations, the MESP surfaces of biguanide's neutral, cationic, and anionic forms were discovered to be comparable. Understanding the pharmacophoric characteristics and complementary surfaces necessary for drug-receptor interactions depends on this commonality.

3.2.4. Stability and Conformational Analysis:

The study identified the most stable conformers of biguanide derivatives through conformational searches, highlighting the importance of specific substituents at the N6 position for achieving energy minimum conformations.

3.2.5. Protonation and Deprotonation Energies:

High-accuracy ab initio calculations were used to estimate the energies associated with protonation and deprotonation processes, providing insights into the stability and reactivity of different biguanide forms.[19]

These findings contribute to a better understanding of the pharmacological properties of biguanide derivatives and their potential applications in medicinal chemistry.

3.3 Comparison of various states for molecular electrostatic potential surface in biguanide:

The molecular electrostatic potential (MESP) surfaces of biguanide derivatives in different states (neutral, protonated, and deprotonated) provide valuable insights into their electronic properties and potential interactions with biological targets. Here are the key comparisons and findings regarding the MESP surfaces in different states:

3.3.1. Similarities across States:

In the most stable configurations, the MESP surfaces of biguanide in its neutral, protonated, and deprotonated forms were shown to be comparable.This suggests that despite changes in charge state, the overall electronic distribution remains relatively consistent, which is important for understanding how these compounds interact with their targets.

3.3.2. Charge Distribution:

The MESP analysis revealed regions of positive and negative charge on the surfaces.Areas of excess electron density are shown by regions of negative charge, and areas of electron shortage are indicated by regions of positive charge. This distribution is crucial for predicting how biguanide derivatives will interact with biomolecules, as drug-receptor interactions are often driven by electrostatic complementarity.

3.3.3. Electrostatic Complementarity:

The study emphasized the importance of understanding the electrostatic complementarity between the MESP of biguanide derivatives and the active sites of biomolecules. The MESP surfaces can help identify potential binding sites and the nature of interactions that may occur during drug-receptor binding.

3.3.4. Impact of Protonation and Deprotonation:

The MESP surfaces change with protonation and deprotonation, reflecting the altered charge distribution and potential reactivity of the biguanide derivatives. For instance, protonation typically increases the positive charge density, which can enhance interactions with negatively charged regions of biological targets.[20]

4. ESTABLISHED MECHANISM OF ACTION

4.1. Metformin and Type 2 Diabetes

4.1.1 Mechanism of action:

Metformin functions as an anti-diabetic agent through several mechanisms:

- **Reduction of Hepatic Glucose Production:**

Metformin helps reduce blood glucose levels by mainly reducing the liver's synthesis of glucose. It prevents the liver from producing glucose from non-carbohydrate sources, a process known as gluconeogenesis.[21]

- **Increased Insulin Sensitivity:** Metformin enhances the sensitivity of peripheral tissues (such as muscle) to insulin, facilitating better uptake of glucose from the bloodstream into the cells. This action helps to lower blood sugar levels.[22]

- **Decreased Intestinal Absorption of Glucose:**

Metformin may also reduce the amount of glucose absorbed from the gastrointestinal tract, contributing to lower postprandial (after meal) blood glucose levels.[23]

- **Activation of AMP-Activated Protein Kinase (AMPK):**

The enzyme AMPK, which is essential for maintaining cellular energy balance, is activated by metformin. This activation leads to various metabolic effects, including the inhibition of lipogenesis (fat production) and the promotion of fatty acid oxidation, which can further improve insulin sensitivity.

These combined effects make metformin a potent and widely used first-line treatment for individuals with type II diabetes.[24] .The indication of metformin and its major side effect lactic acidosis data has been displayed in table 1 & 2 ,3

4.1.2 Clinical efficacy and safety profile [25]

Tables.1

INDICATION FOR USEs	DIET-FAILED NIDDM, ESPECIALLY IF OVERWEIGHT. FAILURE TO MEET TREATMENT GOALS ON SULFONYLUREA THERAPY

TYPE OF USE	COMBINING MONOTHERAPY WITH A SULFONYLUREA
DOSAGES AVAILABLE	500 MG and 850 MG
TREATMENT SCHEDULE	TAKE WITH MEALS, GRADUALLY INCREASE DOSAGE, AND DON' EXEED 3 GRAMS PER DAY.
CONTRAINDICATIONS	ANY HYPOXIC CONDITION, HISTORY OF LACTIC ACIDOSIS, ALCOHOL ABUSE, RENAL AND HEPATIC DISEASES AND CARDIAC INSUFFICIENCY.
SUGGESTED PRECAUTIONS	EXAMINE LIVER FUNCTION, CREATININE, AND POSTPARTUM LACTATE ONCE OR TWICE A YEAR.
SIDE EFFECTS	DIARRHEA, METALLIC TASTE, NAUSIA, ANOREXIA AND FIRST GASTROINTESTINAL UPSETS
ADVERSE REACTION	LACTIC ACIDOSIS IN THE EVENT OF SERIOUS IMPAIRMENT OF HEPATIC OR RENAL FUNCTION. TAKING A SULFONYLUREA OR ABUSING ALCOHOL MIGHT CAUSE HYPOGLYCEMIA..

Table.2 Metformin Associated Lactic Acidosis

	APPROXIMATE NUMBER OF PATIENT YR OF TREATMENT	TOTAL CASES (NONFATAL/FATAL)	INCIDENCE (TOTAL CASES/1000 PATIENT YR)	MORTALITY RAIT (FATAL CASES/1000 PATIENT YR
UK (1976-86)	400,000	11 (4/7)	0.027	0.017
SWITZERLAND (1972-77)	29,800	2 (2/0)	0.067	--------
CANADA (1972-82)	56,000	0	-------	-------
SWEDEN (1972-81)	83,500	7(5/2)	0.084	0.024

Table.3 Phenformin-Associated Lactic Acidosis

SWITZERLAND (1972-77)	6,200	4 (1/3)	0.64	0.48
SWEDEN (1975-77)	20,000	13 (7/6)	13 (7/6)	0.30

4.2. Other approved or traditional applications

Biguanides have several important applications in medicine, including:

- **Anti-Diabetic Agents:** By decreasing the synthesis of glucose in the liver and enhancing insulin sensitivity in muscle tissues, biguanides—in particular, metformin—are frequently used as hypoglycemic medications to treat type II diabetes.
- **Antiseptics**: They have been utilized for their antiseptic properties, helping to prevent infections.
- **Antimalarials:** Some biguanides have shown effectiveness in treating malaria.
- **Serotoninergic Antagonists:**They are also known to act as serotoninergic antagonists, which can have implications in treating various psychiatric conditions.
- **AntitumoralAgents:**Because of their capacity to alter cellular metabolism, biguanides have been studied for their potential in the treatment of cancer.

Coordination Chemistry: Their efficacy in chelating metals has made them useful in coordination chemistry applications. These diverse applications highlight the versatility and importance of biguanides in the medical Sciences [26]

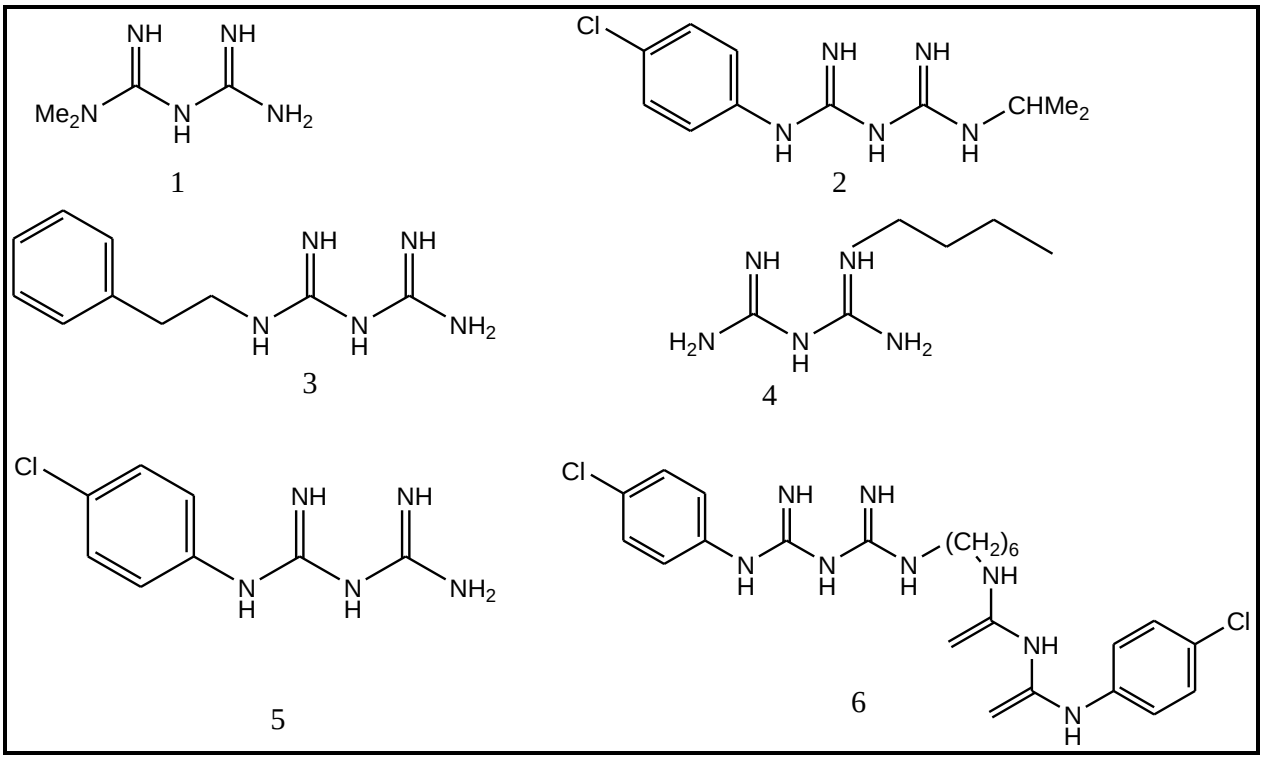

Figure. Various medicinally important biguanide compounds

5. EMERGING APPLICATIONS

5.1. Cancer Therapy

- Biguanides' anti-tumor capabilities were unknown until 2005, when Evans et al. found an inverse relationship between metformin medication and cancer incidence in diabetic individuals. This finding opened the door for research into the use of biguanides in cancer prevention and therapy.
- Anti-tumor effects: inhibition of mitochondrial respiration, impact on mTOR signaling, and potential in combination therapies.
- In general, biguanides are believed to exert their antitumor properties by two main mechanisms: direct, by acting directly on the tumor cells and inhibiting their growth, and indirect, by inducing changes in the body that ultimately affect tumorigenesis.[27]

5.2. Aging and Longevity

- Metformin,whichisthemostcommonlyusedoraldrugfortype2diabetes,hasmanyothermechanismsofaction.Itsantiaging effectworksonmanyorgansinourbodies,whichgiveshopetofindnti-agingsubstance.However,manydetailed,multicentre,randomizedtrialsareneededtodeterminetheexactanti-agingdose,itspossiblesideeffects,aswellasitseffectsonvariousorganisms.[28]

5.3. Cardiovascular Diseases

- Comparing the long-term effects of biguanides with DPP-4 inhibitors on diabetes-related complications, cardio-cerebrovascular events, and related expenses has not been well studied.
- A more thorough assessment of particular anti-diabetes treatments in those with high cardiovascular risk is given by recent cardiovascular research.
- Metformin's continued usage as a first-line medication is supported by historical evidence. GLP-1 receptor agonists and DPP-4 inhibitors seem to have little effect on cardiovascular outcomes. The remarkable reduction in cardiovascular risk linked to empagliflozin SGLT-2 inhibitor medication may influence physicians' recommendations for further treatment in addition to metformin.[29]

5.4. Polycystic Ovary Syndrome (PCOS)

- The newer insulin sensitisers, such as isothiols, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl pepdidase-4 (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGLT2) inhibitors, are the foundation of the most recent treatment of POCS.
- Polycystic ovaries, chronic anovulation, and hyperandrogenism are the hallmarks of PCOS, the most prevalent endocrinopathy in women. PCOS is primarily treated symptomatically with lifestyle changes and drugs like Metformin, oral contraceptives, and antiandrogens.[30]

5.5. Neurological Disorders

- Targeting trace amine-associated receptors (TAARs), trace amines (TAs) are endogenous neuromodulators that contribute to synaptic transmission in the central nervous system (CNS).
- According to recent research, a number of antidiabetic medications can increase neuronal lifespan and significantly improve memory and cognition in a variety of clinical contexts.
- Thiazolidinediones, metformin, and the more modern drugs that target the glucagon-like peptide-1 receptors
- Thus far, there is compelling evidence that these antidiabetic medications may be developed as disease-modifying treatments for brain disorders in both diabetic and non-diabetic individuals.[31]

6. METFORMIN'S STRUCTURE RELATES TO ITS FUNCTION AS A TREATMENT FOR TYPE II DIABETES:

Metformin's structure is closely related to its function as a treatment for type II diabetes in several ways:

6.1. Biguanide Structure:

Metformin is a member of the biguanide class of compounds, characterized by the presence of two guanidine groups. This structural feature is essential for its biological activity, as it allows metformin to interact with various enzymes and receptors involved in glucose metabolism.

6.2. Inhibition of DihydrofolateReductase (DHFR):

Metformin has been shown to competitively inhibit the enzyme Escherichia coli dihydrofolatereductase (ecDHFR). This inhibition can disrupt folate metabolism, which is linked to the regulation of pyridine nucleotide pools that are crucial for cellular energy metabolism. By affecting these metabolic pathways, metformin can help lower blood glucose levels.

6.3. Mimicking Folate:

The structural similarity of metformin to folate allows it to mimic folate in its interactions with DHFR. This mimicry may contribute to its anti-folate activity, which can have downstream effects on cellular metabolism and energy homeostasis, further supporting its role in managing diabetes.

6.4. Targeting Mitochondrial Pathways:

Metformin's structure enables it to target mitochondrial complex I, which plays a critical role in cellular respiration and energy production. By inhibiting this complexmetformin improves insulin sensitivity and decreases the synthesis of glucose in the liver which are key mechanisms in the management of type II diabetes.

6.5. Gut Microbiome Interaction:

The structure of metformin also allows it to interact with the gut microbiome, which has been recognized as an important mediator of its effects. The drug's presence in the gastrointestinal tract can influence microbial composition and activity, contributing to its glucose-lowering effects,[32]

In summary, metformin's structural characteristics facilitate its interaction with various biological targets, leading to multiple

mechanisms of action that collectively contribute to its efficacy in treating type II diabetes.

7. SIDE EFFECTS AND LIMITATIONS

There are some limitations with bigunanides. Some of them are acute heart failure, functional hepatic failure, chronic kidney disease, or chronic liver diseases. Infrequently some patient diagnosed with lactic acidosis.Some time acute pancriatities also appears as a side effect.

PHMB, a polymeric biguanide, is used to clean contact lenses, sterilize medical equipment, and irrigate wounds. Biguanides, primarily metformin, are currently being researched to treat a variety of cancers, including breast cancer.There are also some limitations mentioned.

8. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Despite having very appealing pharmacological features, the biguanide class of chemicals is still poorly understood, and only a small number of bioactive analogs have been produced. However, compared to the investigated chemical space, the number of biguanide medications that have been successful is extremely considerable.

9. CONFLICT OF INTEREST

The authors declare no conflict of interest .

10. CONCLUSION

In conclusion, biguanides represent a diverse and valuable class of compounds with significant therapeutic potential beyond their well-established role in treating type 2 diabetes. Despite their widespread use, the lack of comprehensive structural and mechanistic understanding has hindered the full exploration of their pharmacological actions. Their versatility as reaction catalysts, strong organic bases, and metal ligands further underscores their importance in drug development and organic synthesis. Continued research into the electrical and structural properties of biguanide derivatives may uncover novel mechanisms of action and expand their applications in various therapeutic areas, including antimalarial, anticancer, antiviral, and antibacterial treatments.

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